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Effect of Simvastatin on Alcohol Induced Hepatitis in Experimental Rat

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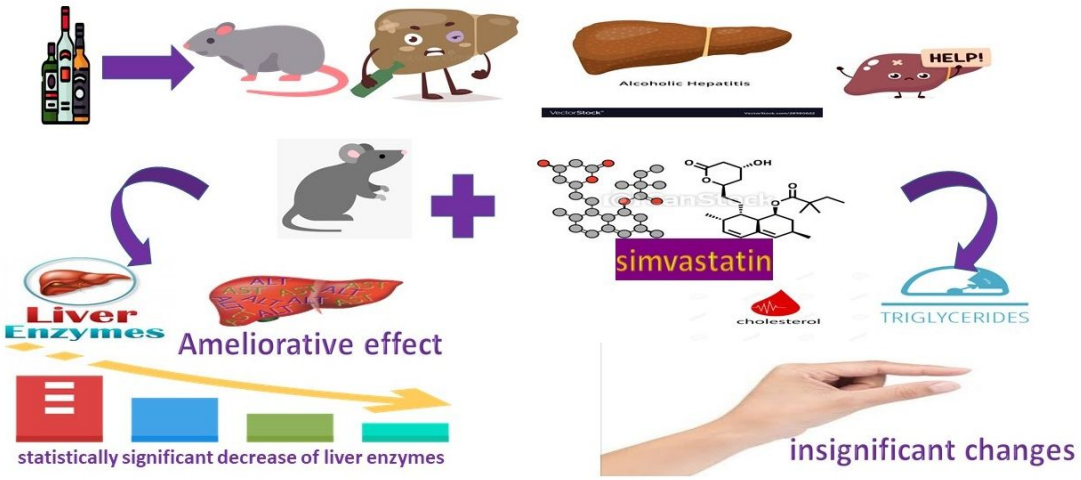
Graphical Abstract



Abstract

Alcohol consumption is a major public health concern around the world, and it is one of the risk factors for liver diseases. There are currently no Food and Drug Administration FDA-approved drugs to prevent or cure alcohol-induced liver disease (ALD) at any stage. Consequence, therapeutic solutions are still a key requirement for those patients. The current study was intended to evaluate the effect of simvastatin in ethanol induced hepatitis and its progression. We demonstrated that chronic drinking of ethanol significantly elevated liver enzymes which were decrease upon simvastatin treatment, indicating its ameliorative effect. TG level was increased in alcohol induced hepatitis group when compared to normal control group and supplementation with simvastatin showed insignificant decrease of serum TG. However, there is insignificant change in the serum total cholesterol in the present model of alcohol induced hepatitis and the results represent the reversal of hypercholesteremia after 55 days. These results suggest simvastatin could prove not beneficial in the prevention or treatment of ALD.

Keywords: Simvastatin - Alcohol induced hepatitis, Liver disease, Ameliorative effect

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1. Introduction

Alcoholic liver disease (ALD) continues to be a major source of morbidity and mortality, with more than 75,000 deaths worldwide each year and an increase in incidence over the last decade [1]. (ALD) is associated with a wide range of liver disorders, from fatty liver to steatohepatitis and liver fibrosis/cirrhosis. Hepatocyte death caused by oxidative damage in ethanol poisoning is thought to be the most obvious cause of ALD [2]. Simvastatin is a lipid-lowering medication that inhibits 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. It's a common first-line treatment for lowering cholesterol and preventing coronary heart disease and atherosclerosis (2). In recent years, a considerable number of research have studied the different statins effects, such as anti-inflammation, immunoregulation, anti-apoptotic activity, and autophagy induction by decreasing cytokines like tumor necrosis factor- Alfa (TNF-α) and caspase-3 [3, 4]. This study designed to evaluate the effect of simvastatin in ethanol induced hepatitis and its progression.

2. Materials and Methods

2.1. Experimental animals

Adult male Sprague Dawley rat were purchased from the National Cancer Institute (NCI) (Egypt), their weight ranged from150 to 200g. The rats were housed in ideal conditions, with free access to food and water. One week prior to the start of the experiment, the rat was allowed to acclimate to laboratory settings. The animal ethical committee of Suez Canal University approved the study plan.

Table 1: Results of liver enzymes in all studied groups under study

Groups (n= 10)	ALT (U/L)	AST (U/L)	AST/ALT
1	20±13	15.7±13	0.78±0.05
2	22±12	20.29±7.5*	0.92±0.05**
3	66.2 ±18*	171.4±9.8*	2.58±0.06*
4	212.6±4*	154.73±15*	0.72± 0.05
5	141±18*	130.11±3.9*,**	0.92±0.03**

(*) refer to allgroups compare with GP1,
(**) refer to allgroups compare with GP2.

2.2. Experimental design

The present study was carried on 70 rats, they separated into a control group and four experimental groups: **Gp. 1** (control group): (10 animals) were received a typical diet. **Gp. 2**: (10 animals) were received orally (gavage) simvastatin (10mg\kg\day), for 55 days. **Gp. 3**: (10 animals) were received orally (gavage) ethanol (6.5 g/kg/day, 22.5% w/v), for 55 days. **Gp. 4**: (20 animals) were received orally (gavage) ethanol (6.5 g/kg/day, 22.5% w/v) + simvastatin (10mg\kg\day) once a day, for 55 days. **Gp. 5**: (20 animals) received orally (gavage) ethanol (6.5 g/kg/day, 22.5% w/v) for 55 days & then received simvastatin (10mg\kg\day) once a day after initiation of alcoholic hepatitis for 55 days.

2.3. Blood sampling

Animals were sacrificed under anesthesia by diethyl ether at the end of the experiment (55 day), and blood samples were taken in a plain test tube to separate serum for biochemical analysis.

Table 2: lipid profile in all studied groups under study

Groups (n= 10)	CHOL (mg/dL)	Tg (mg/dL)
1	119.7 ± 8.9	139 ± 40.46
2	136.9 ± 3.9	135.4 ± 13.9
3	127.4 ± 5.3	225.2 ±11.7*
4	124 ± 10.9	205.4 ± 5.5*
5	157.8 ± 5.7	201.3 ± 3.4*

2.4. Biochemical studies

The separated serum was used determine aspartate aminotransferase [5], alanine aminotransferase [6] activities, total cholesterol [7], and triglyceride levels [8].

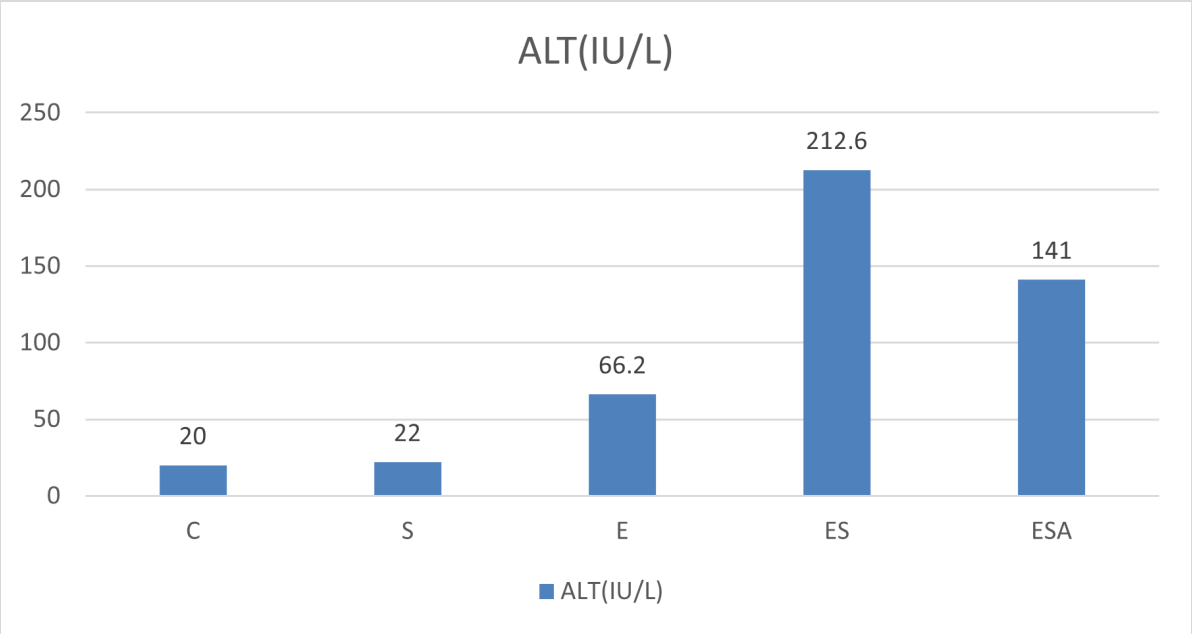

Figure 1: Results of ALT in allstudied groups under study. Gp.1: received a standard diet.
Gp.2: received orally simvastatin (10mg\kg\day).
Gp.3: received ethanol (6.5 g/kg/day, 22.5% w/v).
Gp.4: received orally ethanol+ simvastatin.
Gp.5:received orally ethanol (6.5 g/kg/day, 22.5% w/v)once a day for 55 days & then received simvastatin (10mg\kg\day) once a day after development of alcoholic hepatitis for 30 days.

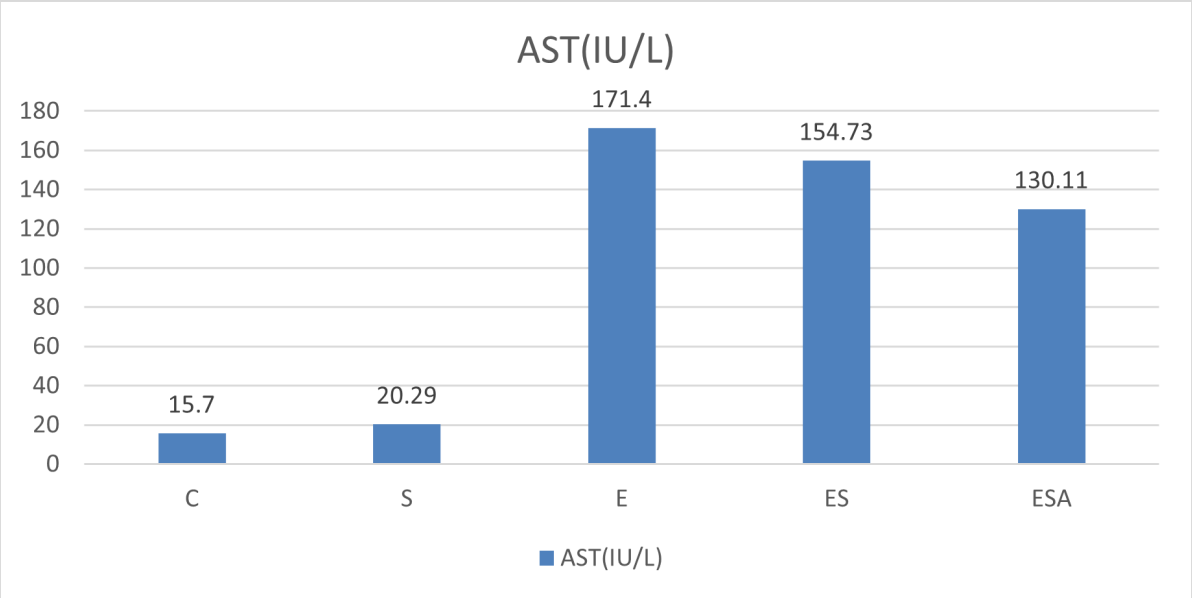

Figure 2: Results of AST in allstudied groups under study. Gp 1: received a standard diet.
Gp 2: received orally simvastatin (10mg\kg\day).
Gp 3: received ethanol (6.5 g/kg/day, 22.5% w/v).
Gp 4: received orally ethanol+ simvastatin.
Gp 5:received orally ethanol (6.5 g/kg/day, 22.5% w/v)once a day for 55 days & then received simvastatin (10mg\kg\day) once a dayafter development of alcoholic hepatitis for 30 days.

2.5. Statistical analysis

The data is displayed as mean ± standard error (SE). Statistical analyses carried out using the SPSS 16 software package [9].

3. Results and discussions

3.1. Liver enzymes results:

There is a significant increase in liver enzymes in ethanol feeding groups. We found that chronic-binge ethanol feeding suggestively elevated serum ALT and AST levels and AST: ALT ratio more than 1. Meanwhile, upon simvastatin treatment, the treated group showed a statistically significant decrease of liver enzymes indicating its ameliorative effect. (Table 1). The diagnosis of alcoholic hepatitis is straightforward by evidence of liver functional impairment, such as elevation of ALT and AST levels may be the only diagnostic clue. We demonstrated that chronic-binge ethanol feeding significantly elevated serum ALT and AST levels and AST: ALT ratio more than 1 [10, 11]. Meanwhile, upon simvastatin treatment, the treated group showed a statistically significant decrease of liver enzymes indicating its ameliorative effect. The results revealed low ALT and AST levels in the ethanol-treated group with the lowest levels observed in ethanol group that was co-treated with simvastatin [12].

3.2. Lipid profile results:

TG level was increased in alcohol induced hepatitis group when compared to control group. Supplementation with simvastatin to ethanol fed rats showed insignificant decrease of serum TG. In our study, addition of simvastatin to ethanol fed rats showed insignificant decrease of serum TG. Inconsistently with previous findings demonstrated that simvastatin is effective in decreasing TG levels in co-administration of simvastatin and alcohol in rats [13]. However, there is insignificant change in the serum total cholesterol in the present model of alcohol induced hepatitis and the present conclusions represent the reverse of hypercholesteremia after 55 days. The insignificant change in the serum total cholesterol in the present model of alcohol induced hepatitis is reasonably expected since liver biosynthesis has been reduced [14]. The present findings represent the reversal of hyperlipemia after 55 days as a result of decreased function of cholesterol binding reserve. The abnormal levels of cholesterol binding reserve may indicate the initiation of risk factors manifest with hyperlipemia followed by transition from fatty liver to more advanced lesions and

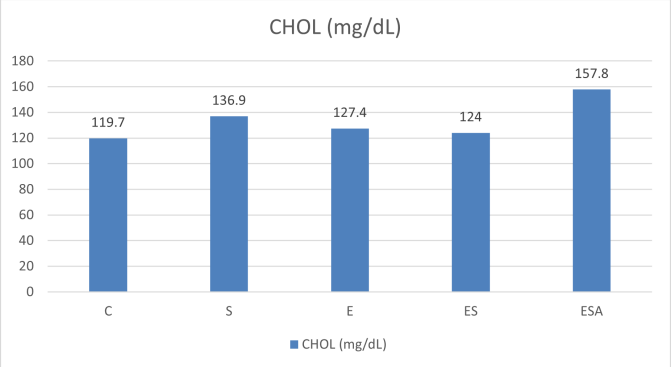

Figure 3: CholesterolResults in all studied groups under study. Gp.1: received a standard diet.
Gp.2: received orally simvastatin (10mg\kg\day).
Gp.3: received ethanol(6.5 g/kg/day, 22.5% w/v).
Gp.4: received orally ethanol+ simvastatin.
Gp.5: received orallyethanol (6.5 g/kg/day, 22.5% w/v) once a day for 55 days & then receivedsimvastatin (10mg\kg\day) once a day after development of alcoholic hepatitis for 30 days.

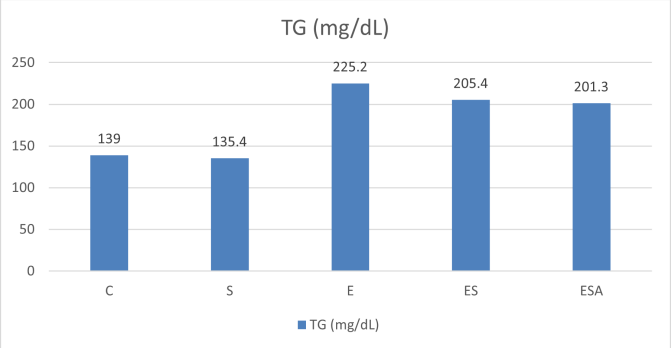

Figure 4: TG results inall studied groups under study.
Gp.1: received astandard diet.
Gp.2: received orally simvastatin (10mg\kg\day).
Gp.3: received ethanol (6.5 g/kg/day, 22.5% w/v).
Gp.4: received orally ethanol+ simvastatin.
Gp.5: received orally ethanol (6.5 g/kg/day, 22.5% w/v) once aday for 55 days & then received simvastatin (10mg\kg\day) once a day afterdevelopment of alcoholic hepatitis for 30 days.

damage [15]. In line with these results, previous studies have demonstrated that increased serum triglyceride in chronic alcohol ingestion [16, 17]. Increased serum TG levels in ethanol-treated rats could be related to reduced lipoprotein lipase activity, which is important in the uptake of TG-rich lipoproteins by extra hepatic tissues.

4. Conclusions

In the present study, supplementation with simvastatin to ethanol fed rats showed insignificant decrease of serum TG. However, there is insignificant change in the serum total cholesterol in the present model of alcohol induced hepatitis and the present findings represent the reversal of hypercholesteremia after 55 days.

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